(c) Labeling claims for specific combinations—(1) Claims for combinations of anticholinergic with opiates. The Panel concludes that claims for enhanced effectiveness of the opiates through combination with atropine or its derivatives is not supported clinically or theoretically, since large and potentially toxic doses of the anticholinergics are required for partial suppression of the increased tone of the ileum and colon induced by morphine (Ref. 1). For example, the addition, in a non-OTC drug, of atropine at only 1/20 of the usual effective dose (0.025 mg./tablet) to diphenoxylate is widely recognized as an example of additive toxicity without additive therapeutic benefit (Ref. 2).

REFERENCES

(1) Adler, H. F., A. J. Atkinson and A. C. Ivy, "Effect of Morphine and Dilaudid on the Ileum and of Morphine, Dilaudid and Atropine on the Colon of Man," Archives of Internal Medicine, 69:974-85, 1942.

(2) Rosenstein, G., M. Freeman, A. Standard and N. Weston, "Warning: The Use of Lomotil in Children," Pediatrics, 51:132-133, 1973.

(2) Claims for combinations of antidiarrheals with antacids. Some antidiarrheal combination products contain various amounts of effective antacid ingredients as calcium carbonate, calcium hydroxide and hydrated alumina powder, as well as antidiarrheal ingredients. It is well known that many effective antacids including those listed above when given in adequate doses for antacid therapy will sometimes cause mild constipation. The fact that these agents may cause constipation when used in antacid therapy, does not constitute a rational basis for the claim that these agents are also effective antidiarrheals. In addition, there is no known relationship between gastric secretion and constipation. Thus, the Panel is of the opinion that it is not rational concurrent therapy for a significant portion of the population for the label to claim both antacid and antidiarrheal properties if the antidiarrheal claim is supported by a nonantidiarrheal ingredient.

(3) Conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below:

ADSORBENTS

Attapulgite, activated

Charcoal, activated

Kaolin

Pectin

ANTICHOLINERGICS

Atropine sulfate

Homatropine methylbromide

Hyoscyamine sulfate

ASTRINGENTS

Alumina powder, hydrated

Bismuth salts

Calcium hydroxide

Phenyl salicylate (salol)

Zinc phenolsulfonate

OTHER CLAIMED ACTIVE INGREDIENTS

Calcium carbonate

Lactobacilli

Acidophilus

Bulgaricus

Sodium carboxymethylcellulose

LABELING CLAIMS FOR SPECIFIC INGREDIENT

Bismuth subsalicylate

The Panel believes it reasonable to allow 2 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed as active anti-diarrheal ingredients in over-the-counter products but may be permitted as inactive ingredients if the amount employed is shown to be free of pharmacologic or toxic effect and contributes to the pharmaceutical formulation of the product. Some ingredients may be present in products in quantities which are pharmacologically inactive by virtue of being subclinical doses. In these cases, the ingredients may be included for pharmaceutical necessity or convenience, such as improving the stability or palatability of the product. However, it is the opinion of the Panel that if an ingredient was originally claimed by the sponsor to be active, it cannot then also be claimed inactive and included for formulation purposes unless the following are documented: The absolute necessity for inclusion in the pharmaceutical formulation, the safety of the quantity in the finished product, and the inactivity of the quantity in the finished product.

The Panel stongly recommends that all inactive ingredients be listed with or without a statement of their quantity, since the consumer may need to know for a variety of reasons, the ingredient in a product. However, the product cannot be promoted on the basis of its inactive ingredients, nor can the label emphasize the inclusion of the inactive ingredients.

The Panel has given careful consideration to the types of studies and types of data to be required for removing a claimed active antidiarrheal ingredient from Category III and placing it in Category I. (See paragraph I below for data required for antidiarrheal ingredient evaluation). In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blind study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of general population as well as diet, activity, travel, etc., of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredients (e.g., stool frequency, stool volume, stool weight, stool water content, stool consistency, etc.). To demonstrate safety, appropriate toxicological studies in experimental animals (preferably primate) and man are required as outlined elsewhere.

(a) Claimed active ingredients classified as adsorbents--

(1) Attapulgite, activated. The Panel concludes activated attapulgite is safe in the amounts taken orally (e.g., 6 to 9 grams per 24 hour period) but there is insufficient evidence to classify it as an effective antidiarrheal.

Attapulgite is a naturally occurring aluminum magnesium silicate, similar to kaolin. It is inert and, presumably, nontoxic when administered orally (Ref. 1). In experimental animals, no LD_{50} could be obtained at 900 times the clinical dose. There have been few clinical studies on the safety or efficacy of attapulgite (Refs. 2 and 3). One well-controlled study showed that a combination of attapulgite and pectin was more effective than a placebo of unknown composition (Ref. 4). The claimed action of attapulgite is apparently due to its adsorptive properties (Ref. 5), i.e., adsorption of bacteria, toxins, etc.

Data Pertinent for Effectiveness

The Panel recognizes that attapulgite is generally recognized as safe in the amounts taken orally, but adequate data to establish effectiveness are lacking. Additional in vivo and in vitro studies are needed to establish that the primary mechanism of action is that of adsorption. Additionally, well-designed and carefully controlled clinical studies are necessary to establish the effectiveness of attapulgite when compared to placebo and/or an effective antidiarrheal. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Gaubert, Y., "A New Intestinal Adsorbent Medication," Quest. Medical, 17:990-994, 1964 (French).

(2) Caroli, J. and J. Plessier, "Clinical Study of Attapulgite," Semaine des Hospitaux de Paris, 40:1685-1689, 1964.

(3) Barr, M., "Activated Attapulgite," Journal of the American Pharmaceutical Association, 19:85-87, 1958.

(4) Vernon, W. G., Attapulgite Efficacy Study included in OTC Volume 090133.

(5) Bartell, P., W. Peirzchala and H. Tint, "The Adsorption of Enteroviruses by Activated Attapulgite," Journal of the American Pharmaceutical Association (Scientific Edition), 49:1-4, 1960.

(2) Charcoal, activated. The Panel concludes activated charcoal to be safe in the amounts taken orally, but believes there is a lack of acceptable clinical evidence to establish its effectiveness as an antidiarrheal agent.

Activated charcoal powder is the residue obtained by the destructive distillation of wood pulp, suitably treated to increase its adsorptive power. Important characteristics of activated charcoal that contribute to its adsorptive capacity are small particle size, large total surface area, and low mineral content. The only generally accepted medicinal use for activated charcoal is as an antidote in

poisoning (Ref. 1), although it may also prove useful in the treatment of acute hepatic failure (Ref. 2). In regard to its use as an antidote, the adsorbent has been amply demonstrated to bind a number of chemicals within the gastrointestinal tract and thus, prevent their absorption (Ref. 1). Since activated charcoal in the form of tablets or capsules is sometimes recommended for the management of various gastrointestinal disorders such as flatulence and diarrhea (Ref. 3), it is significant to point out that activated charcoal powder has been demonstrated to be much more effective as an adsorbent than activated charcoal tablets (Ref. 4).

Data Pertinent for Safety and Effectiveness

The Panel concurs that activated charcoal is a potent adsorptive agent but there are no partially controlled or controlled clinical studies to establish the effectiveness of activated charcoal as an antidiarrheal agent. Effectiveness should be tested in well-controlled clinical trials comparing activated charcoal with a placebo and/or a known effective antidiarrheal. Dose response data should be established, and, if determined, the effects of an effective dose on the gastrointestinal absorption of various drugs commonly used in small doses (e.g. cardiac glycosides, alkaloids and synthetic estrogens) should be determined. Additionally, data are needed to determine whether activated charcoal contains benzpyrene or methylcholanthrene type carcinogens. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Picchioni, A. L., "Activated Charcoal: A Neglected Antidote," Pediatric Clinics of North America, 17:535-543, 1970.

(2) Gazzard, B. G., et al., "Charcoal Haemoperfusion in the Treatment of Fulminant Hepatic Failure," Lancet, 1:1301-1307, 1974.

(3) Riese, J. A. and F. Damrau, "Use of Activated Charcoal in Gastroenterology: Value for Flatulence and Nervous Diarrhea," Journal of the American Geriatrics Society, 12:500-502, 1964.

(4) Tsuchiya, T. and G. Levy, "Drug Adsorption Efficacy of Commercial Activated Charcoal Tablets in vitro and in Man," Journal of Pharmaceutical Sciences, 61:624-625, 1972.

(3) Kaolin. The Panel concludes kaolin is safe in the amounts taken orally (e.g. 12 to 24 grams per dose), but there is insufficient evidence to classify it as an effective antidiarrheal at this time, nor are there data to establish a dose response relationship.

Kaolin is a native hydrated aluminum silicate, powdered and freed from gritty particles. It is a clay and occurs as a soft white or yellowish white powder. Kaolin is considered to act as an adsorbent and protectant and has been used for over 200 years. It is available only in combination with pectin, or with one or more other antidiarrheals. Kaolin Mixture with Pectin, N.F., is a suspension which contains 20 percent kaolin and 1 percent pectin (Ref. 1). The usual dose is 30 milliliters (6 grams of kaolin, 300 milligrams of pectin). Adequately controlled clinical studies demonstrating the effectiveness of kaolin alone or in combination with pectin are not available. It is considered that kaolin adsorbs some toxins, bacteria, and viruses and is said to provide a protective coating for the intestinal mucosa (Ref. 2). In addition to adsorbing bacteria and various toxins, kaolin may act to increase the resistance of flow by solidifying the colonic contents, although

this has not been demonstrated. As with all adsorbents, kaolin may interfere with the absorption of some drugs, and with vitamins such as thiamine, thus prolonged use may not be advisable (Refs. 3 and 4). A kaolin pectin mixture has been reported to interfere with the gastrointestinal absorption of the antibiotic lincomycin (Ref. 5).

A recent unpublished study submitted to the Panel provided data on the effectiveness of kaolin, pectin, the combination of both, and placebo (water) on a variety of diarrheagenic models in the squirrel monkey (Ref. 5). The dose of active ingredient used was comparable to that recommended for adult humans and based on milliliters per square meter of body surface area. Thus, the dose for a 0.9-kilogram squirrel monkey with a body surface of 0.10 square meter was 3.44 milliliters of kaolin and pectin combination given 3 times daily. The experimental models used to induce diarrhea included (a) A diarrheagenic diet, consisting of oranges, carrots, cabbage ad lib and prune juice instead of drinking water; (b) cholera toxin, in 3 doses; a low dose of 500 mg/kg, a medium dose of 2 gm/kg, and a high (lethal in 48 hours) dose of 4 gm/kg; (c) castor oil, 4 ml/kg; (d) phenolphthalein, 100 mg/kg; (e) methyl prostaglandin E_2, 0.4 mg/kg; (f) bile (beef, dehydrated), 2 gm/kg; and (g) lactulose.

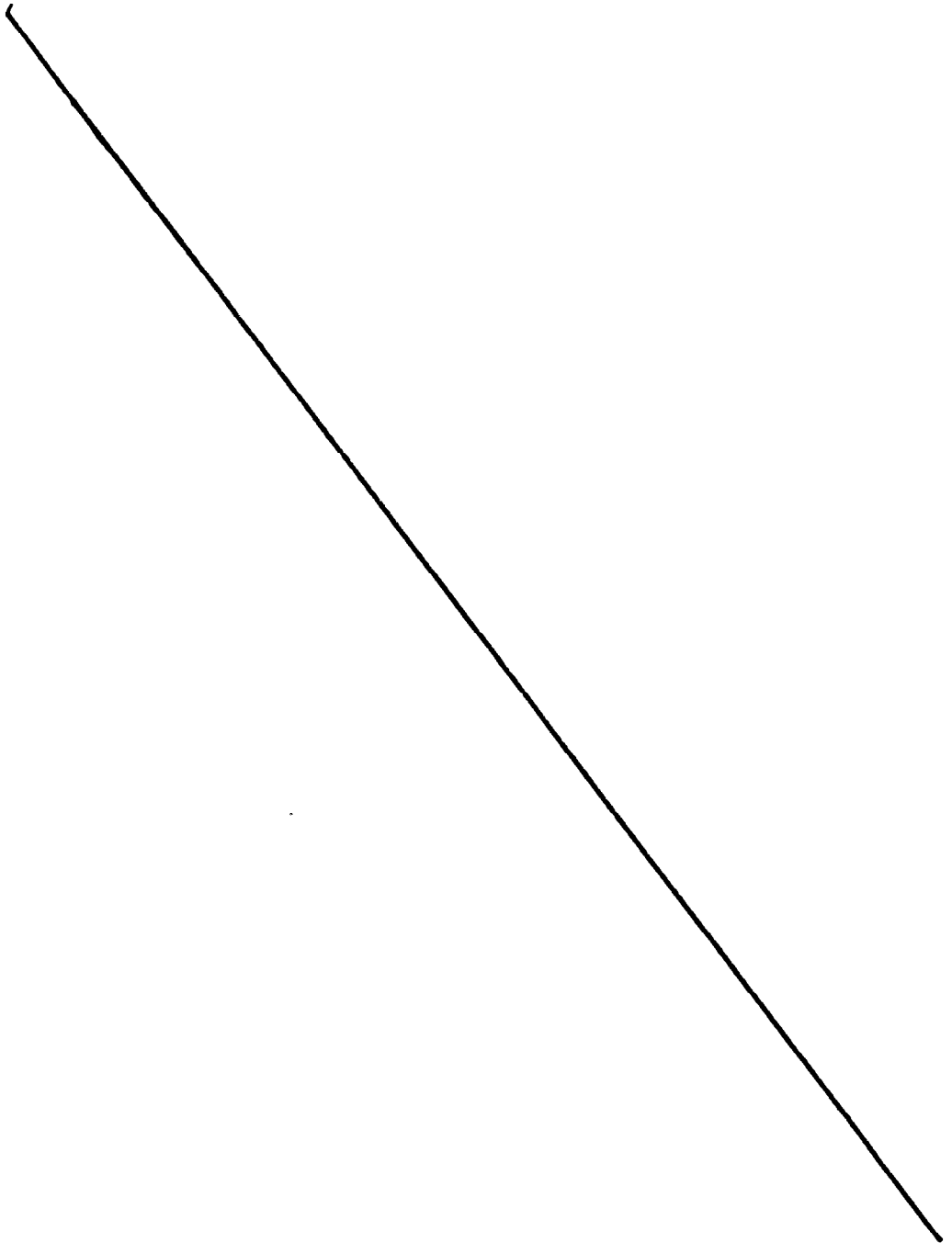
In most of the models studied, it was shown that kaolin, pectin, or the combination of both was more effective in reducing the total number of stools or the number of loose and liquid stools than the placebo. The consistency of the stool was determined by simple observation only. In many of the models, the observed effects can probably be explained by the adsorption of the diarrheagenic agent by the kaolin and pectin. In the diarrheagenic diet model, there was no change in the total number of stools but the number of loose and liquid stools was reduced by kaolin and pectin. In some of the models studied, the diarrheagenic agent did not increase the total number of stools as compared to control periods but the number of loose and liquid stools was increased.

The Panel accepts the results of these studies but questions the relevance of the experimental models to human disease states.

Data Pertinent for Effectiveness Evaluation

The claim that kaolin acts as an adsorbent and protectant should be tested in man using kaolin alone and compared to other known adsorbents. Clinical effectiveness in treatment of diarrhea should be documented by well-designed and controlled clinical trials to test the effectiveness of kaolin alone and

comparisons made with placebo and/or a known effective antidiarrheal. Additional information is needed regarding the interaction of kaolin with other drugs such as cardiac glycosides, antibiotics, alkaloids and vitamins. (See paragraph I below for data pertinent for effectiveness evaluation.)



REFERENCES

(1) The National Formulary, 13th Ed., American Pharmaceutical Association, Washington, DC, p. 388, 1970.

(2) AMA Drug Evaluations, 1st Ed., "Antidiarrheals," American Medical Association, Chicago, p. 579, 1971.

(3) Mann, G. V. and F. J. Stare, "Nutritional Needs in Illness and Disease," Journal of the American Medical Association, 142:409-419, 1950.

(4) Messerli, N., "The Influence of the Addition of Adsorbents to the One-Sided Diet in the Production of Avitaminosis," Archives et Internationales Physiologie de Biochemie, 19:103-114, 1922.

(5) Hansten, P. D., Drug Interactions, 2nd Ed., Lea and Febiger, Philadelphia, p. 131, 1973.

(6) OTC Volume 090121.1/

(4) Pectin. The Panel concludes pectin is safe in amounts taken orally (e.g. 300 milligrams, 3 to 4 times per day), but there is insufficient evidence to establish its effectiveness, nor are there data to establish a dose response relationship.

Pectin is a purified carbohydrate product obtained from the dilute acid extract of the inner portion of the rind of citrus fruits or from apple pomace. It consists chiefly of partially methoxylated polygalacturonic acids. Pectin yields not less than 6.7 percent of methoxy groups and not less than 74 percent of galacturonic acid calculated on a dried basis. Pectin dissolves in 20 parts of water; the resulting colloidal solution is viscous and opalescent, and acid in reaction (Refs. 1 and 2). The mechanism of action of pectin in diarrhea is unknown (Ref. 3). It has been claimed that pectin produces beneficial results because it is an adsorbent and protective agent (Ref. 4). It has also been claimed the beneficial effects are due to lowering the pH by galacturonic acid (Refs. 5 and 6). When fed to healthy human subjects, only a small amount is recovered in the feces because pectin is decomposed in the colon by bacterial action (Ref. 7). In patients with diarrhea, much larger amounts may be eliminated unchanged.

The effectiveness of pectin in various diarrheagenic models in squirrel monkeys has been discussed in the section on kaolin.

Data Pertinent for Effectiveness

The Panel finds insufficient evidence to establish the claimed mechanism of action of pectin as an antidiarrheal agent, i.e. an adsorbent and protective agent. This claim should be tested in man. The effect of pectin on intraluminal pH also has not been well documented. There are no controlled clinical trials substantiating the effectiveness of pectin alone in the treatment of diarrhea in man. Pectin is usually given in combination with kaolin or other antidiarrheal agents. Effectiveness of pectin should be tested against a placebo in well-controlled clinical trails. A comparison should also be made with a known effective antidiarrheal. If pectin acts by physically altering the suspension of kaolin or otherwise enhancing the effect of other antidiarrheals, this should be documented and the dose-ratio established. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation).

REFERENCES

(1) The National Formulary, 13th Ed., American Pharmaceutical Association, Washington, D.C., p. 525-526, 1970.

(2) Swinyard, E. A., "Demulcents, Emollients, Protectives and Adsorbents, Antiperspirants and Deodorants, Absorbable Hemostatics, Astringents, Irritants, Sclerosing Agents,

Caustics, Keratolytics, Antiseborrheics, Melanizing and Demelanizing Agents, Mucolytics, and Certain Enzymes," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, MacMillan Co., New York, p. 990, 1970.

(3) Howard, P. J. and C. A. Tompkins, "Pectin-Agar for Diarrhea in Infants and the Newborn: A Rational, Simple and Effective Treatment," Journal of the American Medical Association, 114:2355-2358, 1940.

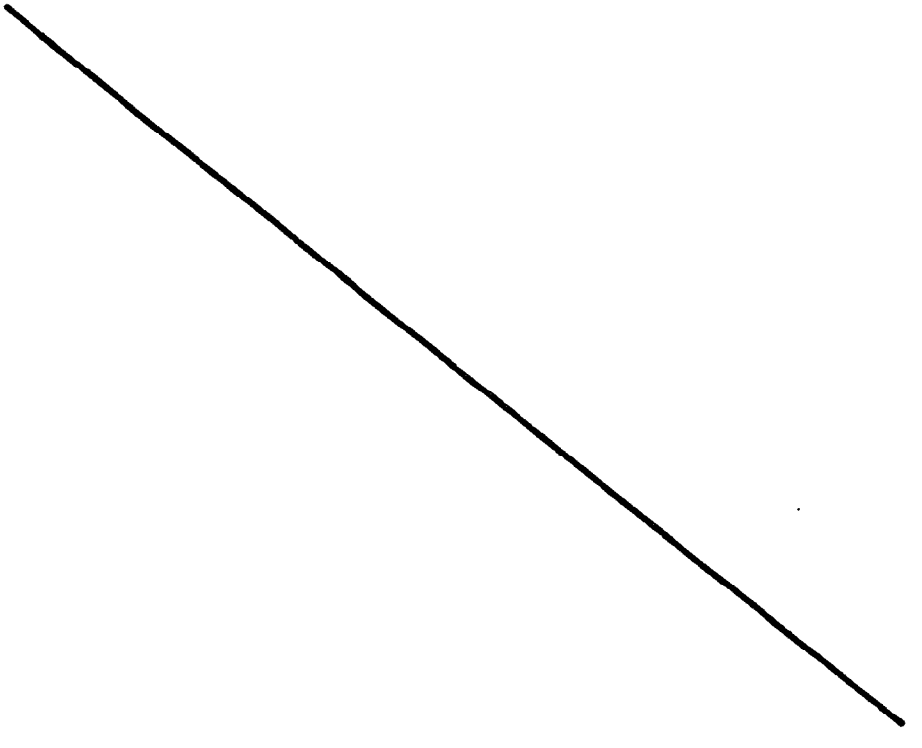
(4) Olsen, A. G., "Pectin Therapy and Pectin Types," American Journal of Digestive Diseases, 7:515-519, 1940.

(5) Haynes, E., C. A. Tompkins, G. Washburn and M. Winters, "Bactericidal Action of Pectin," Proceedings of the Society of Experimental Biology and Medicine, 36: 839-840, 1937.

(6) Steinhaus, J. E. and C. E. Georgi, "The Effect of Pectin, Galacturonic Acid and Alpha Methyl Galaturonate Upon the Growth of Enterobacteriaceae," Journal of Infectious Diseases, 69:1-6, 1941.

(7) Werch, S. C. and A. C. Ivy, "A Study of the Metabolism of Ingested Pectin," American Journal of Diseases of Children, 62:499-511, 1941.

(b) Claimed active ingredients classified as anticholinergics. The Panel concludes that some anticholinergic drugs are effective in reducing gastrointestinal motility when given in doses which are equivalent to 0.6 to 1.0 milligram of atropine sulfate. However, neither atropine sulfate nor any other anticholinergic drug is safe when given in such doses. Further, the effectiveness of such a small dosage (e.g., 1/100 of the effective atropine dose) of these anticholinergic drugs as contained in present combination of OTC antidiarrheal products is not established. Since the safety and effectiveness is not satisfactorily established for OTC use, the Panel recommends that antidiarrheal products containing anticholinergics when given in doses which are equivalent to 0.6 to 1.0 milligram of atropine sulfate be available only by prescription.



(1) Atropine sulfate. The Panel concludes there is insufficient evidence to establish the safety and effectiveness of atropine sulfate.

Atropine sulfate and related belladonna alkaloids significantly reduce the tone and motility of the gastrointestinal tract by producing parasympathetic blockade (Ref. 1). This effect is especially prominent since sympathetic nerve impulses play little or no part in the regulation of intestinal motility and muscle tone. Normal subjects and some patients with gastrointestinal disease exhibit reduced motor activity in the stomach, small and large intestine following full therapeutic doses (0.6 - 1.0 milligram) subcutaneously or orally (Refs. 1, 2 and 3). However, there is insufficient evidence that the small quantities of anticholinergic agents in antidiarrheal products contribute in any way to effectiveness. Atropine toxicity is well established; children are particularly susceptible. Although doses of 500 milligrams have been survived, as little as 10 milligrams have been fatal (Ref. 1).

(2) Homatropine methylbromide. The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of homatropine methylbromide at this time.

Homatropine methylbromide is a quaternary ammonium derivative of belladonna alkaloid which possesses most of the pharmacologic and toxic properties of atropine (Refs. 1, 4, and 5). It is approximately 1/2 as potent as atropine, and it is claimed to be only 1/50 as toxic as atropine (Ref. 1), although this claim is not well documented (Ref. 1).

(3) Hyoscyamine sulfate. The Panel concludes there is insufficient evidence to establish the safety and efficacy of hyoscyamine sulfate.

Atropine is a racemic mixture of equal parts of d- and l-hyoscyamine. The l-form is more potent than d-hyoscyamine. Hyoscyamine sulfate is entirely in the l-form and is, therefore, nearly twice as potent as atropine sulfate in its antimuscarinic effects (Ref. 1).

Labeling

The Panel concurs with the required warning statements for belladonna preparations in the regulations (21 CFR 369.20) which states in part:

> Warning-- Not to be used by persons having glaucoma or excessive pressure within the eye, or by elderly persons (where undiagnosed glaucoma or excessive pressure within the eye occurs most frequently), or by children under 6 years of age, unless directed by a physician. Discontinue use if blurring of vision, rapid pulse, or dizziness occurs. Do not exceed recommended dosage. Not for frequent or prolonged use. If dryness of the mouth occurs, decrease dosage. If eye pain occurs, discontinue use and see your physician immediately as this may indicate undiagnosed glaucoma.

Because of occurrence of severe atropine poisoning in young children, belladonna preparations for OTC use should not contain more than 0.5 milligram atropine equivalent per 15 milliliters or per 15 grams of final preparation.

Data Pertinent for Safety and Effectiveness

The Panel concurs that anticholinergic drugs can be effective in the treatment of diarrhea when administered under the supervision of a physician. The Panel's primary concern is that of safety when anticholinergic drugs are included in OTC antidiarrheal products in quantities that contribute to the antidiarrheal effect of the product. Accordingly, if the safety and effectiveness is not satisfactorily established for OTC use, the Panel recommends that antidiarrheal products containing anticholinergics be available only by prescription. It must be demonstrated by carefully controlled clinical trials that anticholinergic drugs used in OTC antidiarrheals are safe and contribute to the effectiveness of the combination products. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation).

REFERENCES

(1) Innes, I. R. and M. Nickerson, "Drugs Inhibiting the Action of Acetylcholine on Structures Innervated by Postganglionic Parasympathetic Nerves (Antimuscarinic or Atropinic Drugs)," The Pharmacological Basis of Therapeutics, 4th Ed., Edited by Goodman, L. S. and A. Gilman, The MacMillan Co., New York, p. 524-548, 1970.

(2) Bachrach, W. H., "Anticholinergic Drugs: Survey of the Literature and Some Experimental Observation," American Journal of Digestive Diseases, 3:743-799, 1958.

(3) Ingelfinger, F. J., "The Modification of Intestinal Motility by Drugs," New England Journal of Medicine, 229: 114-122, 1943.

(4) Hadfield, W. A., Jr., "The Effect of Homatropine Methylbromide on Human Gastrointestinal Motor Activity," Gastroenterology, 28:642-655, 1955.

(5) Cahen, R. L. and K. Tvede, "Homatropine Methylbromide: A Pharmacological Revaluation," Journal of Pharmacology and Experimental Therapeutics, 105:166-177, 1952.

(c) Claimed active ingredients classified as astringents. Astringents are locally acting drugs that precipitate protein. They are thought to act by reducing cell membrane permeability without cell destruction. A number of organic chemicals and certain metallic ions such as those of zinc and aluminum are said to have astringent properties in high dilution. Many antidiarrheal drugs are claimed to have an astringent action. The Panel was unable to find evidence to support this claim or to demonstrate that astringent properties confer effectiveness in diarrhea.

(1) Alumina powder, hydrated. The Panel agrees with the OTC antacid Panel that hydrated alumina powder is safe in the amounts usually taken orally for antacid therapy (Ref. 1). Doses used for antacid therapy sometimes cause constipation (Ref. 2).

The fact that hydrated alumina powder sometimes causes constipation when used in adequate doses in antacid therapy does not constitute a rational basis for the claim that the agent is also an effective antidiarrheal.

The Panel is unable to find any studies that evaluate aluminum compounds as a single agent for the treatment of acute diarrhea. Nor could any dose-response data relative to the constipating effect be located.

The inclusion of alumina gel in antidiarrheal preparations to maintain kaolin or attapulgite in suspension and allow greater surface area for adsorption may be a reasonable formulation or pharmaceutical necessity but does not justify the claim that it is an active ingredient.

Data Pertinent for Effectiveness

It must be demonstrated in man that alumina powder is an effective antidiarrheal by well-controlled clinical comparisons made with a known effective antidiarrheal and a placebo. If found effective, dose-response data should be obtained. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation).

REFERENCES

(1) "Proposal Establishing a Monograph for OTC Antacid Products," published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714).

(2) AMA Drug Evaluations, 1st Ed., American Medical Association, Chicago, p. 575, 1971.

(2) Bismuth salts (Bismuth subnitrate, bismuth subsalicylate). The Panel concludes that the bismuth subsalicylate is safe in amounts taken orally (0.6 to 2.0 grams of bismuth subsalicylate, 3 to 4 times per day) but there is insufficient evidence to establish effectiveness at this time. There is some question of the safety of bismuth subnitrate. The manufacturer's maximum recommended dose would provide about 5.6 grams for adults and 0.475 gram for children (3 to 6 years old) in 4 hours. Methemoglobinemia in infants has been reported in the literature due to the absorption of nitrates from bismuth subnitrate (Refs. 1 and 2) contraindicating its use in children under 2 years.

Bismuth salts appear to be poorly absorbed from the gastrointestinal tract; several studies report the absence of detectable bismuth in the urine of human subjects given high doses or used over long periods of time. The ingestion

of 30 to 45 milliliters of a liquid bismuth subsalicylate preparation (equivalent to ingesting 5.5 to 8.25 grains (349 to 523.5 mg) of salicylic acid) yielded blood salicylate levels that ranged from barely detectable to 6.2 mg/100 ml.

Data supporting the effectiveness of bismuth in diarrhea are questionable. A ligated calf intestine model was used to study the effect of one bismuth compound on fluid formation by E. coli. Fluid production in the intestinal segment with E. coli and drug was less than with E. coli alone, but the relationship of this model to common diarrhea in humans is unclear. When the drug was administered in vivo to calves with diarrhea, the results indicated that the drug was not effective.

The products are said to provide a coating action. However, two unpublished studies using animals and two using a "gastro-camera" on human subjects failed to demonstrate any clear evidence of a coating action on the mucosa. Reports

attempting to document a coating action for bismuth utilizing a technique of pretreatment with bismuth probably are not applicable, as it can be postulated that the majority of consumers do not use bismuth compounds "prophylactically."

Several clinical trials attempted to document effectiveness of the bismuth compounds in diarrhea. One clinical trial utilized a double-blind technique with a control drug in patients suffering from diarrhea secondary to foreign travel. However, the outcome measurements were based on the patient's subjective opinions of relief (good, excellent, poor, none) with no attempt to standardize the criteria for these responses. Interpretation of the results was difficult. Objective parameters as stool frequency and consistency before and after treatment were not carefully measured (Ref. 3).

Labeling

Special labeling should indicate that stools may become dark with use of any bismuth compound.

Bismuth subnitrate is contraindicated for use in infants under the age of 2 because of the known risk of methemoglobinemia.

Data Pertinent For Effectiveness

Data to date suggest bismuth salts may be effective in mild diarrhea, but the claim needs confirmation by testing in a well-controlled clinical trial using objective parameters to indicate response (e.g number of stools, water content). Bismuth salts should be compared to nonsalicylate containing bismuth salts in order to determine the contribution of salicylate to effectiveness. (See paragraph I below for data pertinent for anti-diarrheal ingredient evaluation.)

REFERENCES

(1) "Accumulation of Nitrate," National Academy of Seiences, Washington, DC, p. 46-75, 1972.

(2) Gleason, M. N., et. al., Clinical Toxicology of Commercial Products: Acute Poisoning, 3rd Ed., Williams and Wilkins, Baltimore, MD, p. 24, 1969.

(3) OTC Volume 090120.[1/]

(3) Calcium hydroxide. The Panel concludes that calcium hydroxide is safe in the amounts taken orally in antidiarrheal products, but there is no evidence of its effectiveness as an antidiarrheal agent.

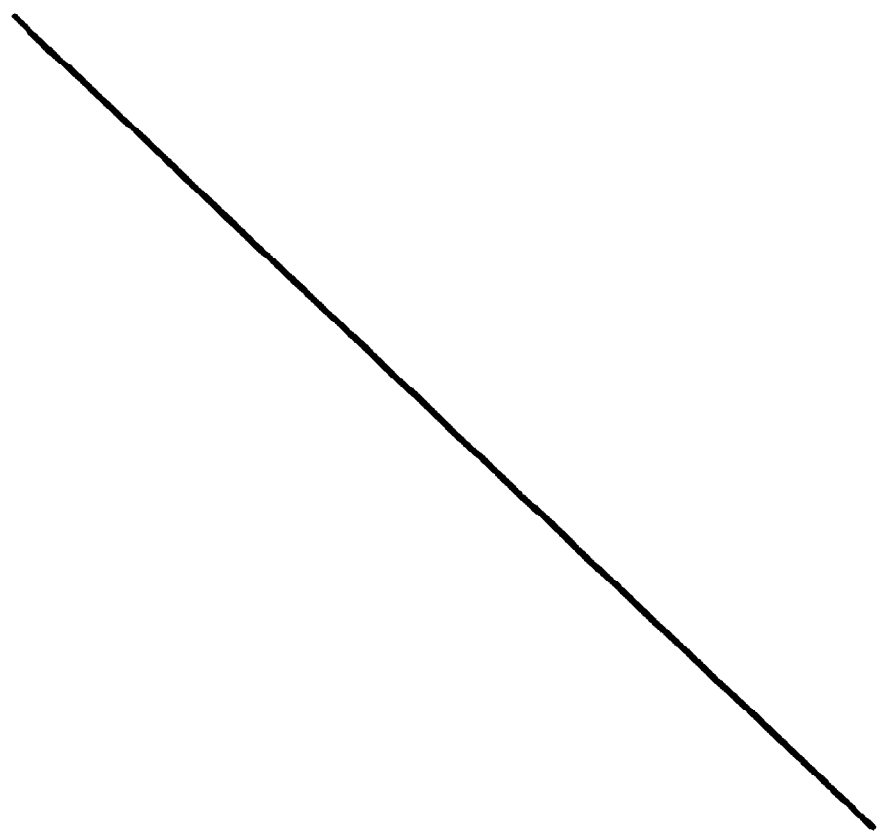
Calcium hydroxide solution, commonly known as lime water, is claimed useful for its antacid properties and for buffering purposes (Ref. 1). The constipating effects of calcium when used as an antacid in moderate doses are well known. However, there is no evidence of effectiveness in the treatment of diarrhea. Calcium hydroxide has been included in multiple ingredient antidiarrheal preparations to provide "temporary relief of gastric discomfort due to overeating and other dietary indiscretions." The Panel is of the opinion that it is not rational concurrent therapy for a significant portion of the population for the label to claim both antacid and antidiarrheal activity if the antidiarrheal claim is supported by a nonantidiarrheal antacid ingredient. (See antidiarrheals discussion above for Category II claims.)

Data Pertinent for Effectiveness

Data are needed on mechanism(s) of action and a dose-response relationship. Effectiveness should be tested in well-controlled clinical trials comparing calcium hydroxide with placebo. Comparison should also be made with a known effective antidiarrheal. (See paragraph I below for data pertinent for antidiarrheal ingredient evalution.)

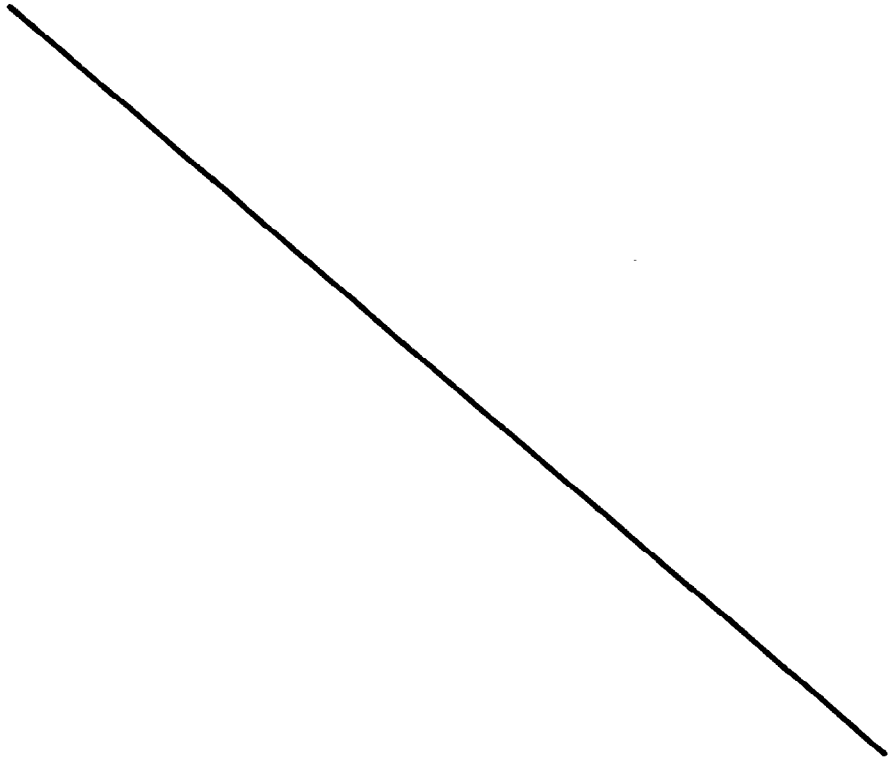
REFERENCES

(1) The Pharmacopeia of the United States of America, 18th Revision, The United States Pharmacopeial Convention, Inc., Washington, DC, pp. 93-94, 1970.



(4) Phenyl salicylate (salol). The Panel concludes that phenyl salicylate is safe in the small amounts taken orally in antidiarrheal preparations, but there is no evidence that it is an effective antidiarrheal.

Phenyl salicylate is no longer listed in the United States Pharmacopeia or National Formulary. The antiseptic utility of salol depended largely on its hydrolysis to phenol and salicylic acid (Ref. 1). However, the decomposition is uncertain or very slow and the absorption of phenol is so rapid that effective concentration of the drug in the alimentary tract is questionable (Ref. 2). The amount of phenol available in salol antidiarrheal preparations is considerably below the 1 to 2 percent phenol solution accepted as bacteriostatic. Giving larger doses of salol could possibly result in phenol poisoning (Ref. 3).



Data Pertinent for Effectiveness

Data are needed on mechanism(s) of action and a dose-response relationship. Effectiveness should be tested in well-controlled, double-blind clinical trials of the antidiarrheal effect of phenyl salicylate (salol) alone and, if desired, in combination as compared with placebo. Comparison should also be with a known effective antidiarrheal. Additionally, measurement of blood salicylate at one hour after dose administration is needed to document the absorption of salicylate. (See paragraph I below for data pertinent for antidiarrheal ingredient evalution.)

REFERENCES

(1) The United States Dispensatory and Physicians's Pharmacology, 26th Ed., Edited by Osol, A., R. Pratt and M. D. Altshule, J. B. Lippincott Co., Philadelphia, PA, p. 899, 1967.

(2) OTC Volume 090053.[1/]

(3) Gleason, M. N., et al., Clinical Toxicology of Commercial Products: Acute Poisoning, 3rd Ed., The Williams and Wilkins Co., Baltimore, p. 113, 1969.

(5) Zinc phenolsulfonate. The Panel concludes that zinc phenolsulfonate is safe in the small amounts usually taken in antidiarrheal preparations, but no evidence exists to establish effectiveness.

The maximal daily adult dose of zinc phenolsulfonate in antidiarrheal products is approximately 400 milligrams. If all of the phenol from zinc phenolsulfonate in antidiarrheal products were absorbed, the amount would be approximately 136 milligrams in a maximum daily adult dose. This figure is well below the reported fatal dose of 1.5 grams (Ref. 1). Therefore, the ingredient seems safe in the small amounts used in antidiarrheal products.

There is no evidence in the scientific literature or modern standard reference texts to establish the effectiveness of zinc phenolsulfonate in the treatment of diarrhea. The sparse information about zinc phenolsulfonate in older editions of textbooks describes the compound as an astringent for topical application to indolent ulcers and subacute inflammation of the nasopharynx or vagina (Ref. 2).

Data Pertinent for Effectiveness

The Panel finds zinc phenolsulfonate safe in the amounts usually taken orally. Effectiveness should be tested in well-controlled, double-blind clinical trails of the antidiarrheal effect of zinc phenolsulfonate alone and, if desired, in combination as compared with placebo. Comparison should also be made with a known effective antidiarrheal. In addition, data are needed on mechanism(s) of action and dose-response relationship. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Gleason, M. N., et al., Clinical Toxicology of Commercial Products: Acute Poisoning, 3rd Ed., Williams and Wilkins, Baltimore, MD, p. 153, 1969.

(2) The Dispensatory of the United States of America, 25th Ed., Edited by Osol, A. and G. E. Farrar, J. B. Lippincott Co., Philadelphia, p. 1519, 1955.

(d) Other claimed active ingredients--(1) Calcium carbonate. The Panel concludes that calcium carbonate is safe in the amounts taken orally for antacid therapy, but can find no evidence that it is an effective antidiarrheal.

The OTC antacid Panel concluded calcium carbonate to be an effective antacid, with the recommendation that not more than 8 grams be taken per day (Ref. 1). The recommendation was based on the knowledge that calcium ingestion can lead to hypercalcuria in some instances. In some individuals, this dose of calcium carbonate can cause constipation (Ref. 2).

The claimed effectiveness of calcium carbonate in acute, self-limiting diarrhea rests on its known constipating effects when used as an antacid in doses of 2 to 4 grams 4 times daily. The Panel could find no dose-response data relative to the constipating effect that could be used to establish dosage as an antidiarrheal. The Panel concludes the constipating effect sometimes observed with effective antacid therapy is not a rational basis for claimed efficacy as an antidiarrheal.

Data Pertinent For Effectiveness

Data are needed on mechanism(s) of action and a dose-response relationship. Effectiveness should be tested in well-controlled clinical trials comparing calcium carbonate with placebo. Comparison should also be with a known effective antidiarrheal. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) "Proposal Establishing a Monograph for OTC Antacid Products," published in the FEDERAL REGISTER of April 5, 1973, (38 FR 8714).

(2) AMA Drug Evaluations, 2nd Ed., American Medical Association, Chicago, p. 787, 1973.

(2) Lactobacillus acidophilus and bulgaricus. The Panel concludes that lactobacillus acidophilus and lactobacillus bulgaricus are safe in the amounts taken orally in antidiarrheal preparations, but finds inadequate

evidence to support their effectiveness as antidiarrheal agents.

In the past 60 years well over 200 papers have reported on the use of lactobacillus acidophilus and lactobacillus bulgaricus in the treatment of diarrhea. Despite the proliferation of studies the very few controlled studies more often show lack of effectiveness than any antidiarrheal effect. The many clinical trials reported are not only uncontrolled but usually ignore the well-defined evidence that establishment of lactobacillus as the dominant fecal flora requires the administration of large amounts (240 to 400 gm) per day of an appropriate carbohydrate such as lactose or dextrin. Dominant colonization, in fact, can be induced by such carbohydrate alone without supplemental lactobacilli (Refs. 1, 2 and 3). Colonization is virtually impossible in the presence of antibiotic therapy; this fact is theoretically inconsistent with the use of lactobacilli to attempt control of antibiotic diarrhea.

The Panel has been informed that additional clinical studies are in progress. In view of this, the Panel finds it appropriate to place lactobacillus in Category III.

Data Pertinent for Effectiveness

The clinical efficacy of lactobacillus should be established in a well-controlled, double-blind study in diarrhea of two or more types. The stool frequency, weight, volume, pH and dominant flora should be included in the evaluation of response of well-matched groups receiving lactobacilli, lactobacilli plus carbohydrate, carbohydrate alone and placebo. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) Cheplin, H. A. and L. F. Rettger, "Studies on Intestinal Implantation of Bacillus acidophilus," Proceedings of the Society of Experimental Biology and Medicine, 17:192-195, 1920.

(2) Conn, H. O. and M. H. Floch, "Effect of Lactulose and Lactobacillus acidophilus on the Fecal Flora," American Journal of Clinical Nutrition, 23:1588-1594, 1970.

(3) Macbeth, W. A. A. G., E. H. Kass and W. V. McDermott, Jr., "Treatment of Hepatic Encephalopathy by Alteration of Intestinal Flora with Lactobacillus acidophilus," Lancet, 1:399-403, 1965.

(3) Sodium carboxymethylcellulose. The Panel concludes that sodium carboxymethylcellulose is safe in the small amounts usually taken orally in antidiarrheal products (200 milligrams 2 to 4 times per day) but that there is insufficient evidence to establish effectiveness as an antidiarrheal agent.

Sodium carboxymethylcellulose is a semisynthetic cellulose derivative which was previously evaluated as a bulk laxative. It is categorized in several texts as a thickening agent to increase the viscosity of various solutions (Refs. 1 and 2). The Panel surmises that increase in the viscosity of the diarrheal fluid and the possible adsorptive qualities might be the rationale for inclusion in an antidiarrheal product. However, the Panel was unable to locate any studies substantiating the effectiveness of carboxymethylcellulose in the treatment of diarrhea at any dose.

Data Pertinent for Effectiveness

The Panel finds sodium carboxymethylcellulose safe in the amounts usually taken orally and would encourage studies to determine effectiveness of a potentially useful antidiarrheal preparation. Effectiveness should be tested in well-controlled clinical trials comparing sodium carboxymethylcellulose with placebo. Comparison should also be made with a known effective antidiarrheal. In addition, data are needed on mechanism(s) of action and dose-response relationship. (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

REFERENCES

(1) The Pharmacopeia of the United States of America, 18th Rev., The United States Pharmacopeial Convention, Inc., Washington, DC, p. 593-594, 1970.

(2) Wilson, C. O., O. Gisvold and R. F. Doerge, Textbook of Organic Medicinal and Pharmaceutical Chemistry, 5th Ed., J. B. Lippincott, Co., Philadelphia, pp. 789, 1966.

(e) Labeling claims for specific ingredient--Bismuth subsalicylate. The Panel concludes that claims that bismuth produces a protective coating that corrects the symptoms of upset stomach, indigestion and nausea are unfounded. The use of a single ingredient for dual or multiple symptoms must be appropriate and rational therapy for a significant proportion of the population. In the case of bismuth subsalicylate, claims of effectiveness for the treatment of a number of symptoms such as nausea, indigestion, upset stomach, etc., in addition to the primary claim as an antidiarrheal, may be rational provided the medication is proven to be effective against each symptom, and there is a significant target population having such concurrent symptoms to justify its use, as for example, individuals suffering from travel related symptoms such as those commonly occuring in the "Turista" syndrome.

Data Pertinent for Effectiveness Evaluation

The Panel concurs with the conclusions of the OTC Antacid Panel in a proposal published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714) that such claims

(nausea, indigestion, upset stomach, etc.) "*** provide evidence of effectiveness consisting of statistically valid clinical trials in relieving each of these symptoms for which a claim is made." (See paragraph I below for data pertinent for antidiarrheal ingredient evaluation.)

G. Products Containing Multiple Antidiarrheal Ingredients

1. General Statements a. The Panel has followed the regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients, and when the combination, when used under adequate direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

b. The Panel conncludes that, in general, the fewer the ingredients, the safer and more rational the therapy. The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

c. The Panel concludes that OTC drugs should contain only such inactive ingredients as are necessary for pharmaceutical formulation.

2. Requirement of significant contribution. The Panel has determined that each claimed active ingredient in the combination must make a significant contribution to the claimed effect. In the absence of data showing the minimum dose necessary to achieve the intended antidiarrheal effect, the amount of ingredient present in antidiarrheal products must be at least equal to the currently accepted minimum dose level for such active ingredients as set forth elsewhere in this document.

The Panel found it impossible to develop a formula for establishing a level below the minimum effective dose level for an ingredient as a single entity at which it could reliably be stated that each antidiarrheal ingredient would make a contribution to a combination drug product. This may be possible with other agents as antacid combination products where the contribution of each antacid can be determined by chemical titration. Antidiarrheals are believed to have a minimum effective dose below which there are few measurable responses. The Panel recognizes that it is possible that some ingredients may be proved to contribute to the effectiveness of a combination product in amounts below the generally recognized minimum effective daily dose. However, because of the numerous variables involved (e.g., differing modes of action, etc.), the Panel could not select one lower level of an active ingredient which may be assumed to be effective in a combination product.

Moreover, the Panel could not establish the percentage of contribution that an active ingredient must make to the effectiveness of the product in order for that contribution to be considered "significant."

The Panel concluded that where a combination product is permitted, as discussed below, it is sufficient to demonstrate in well-controlled clinical trials (Section I below - Data Required for Antidiarrheal Ingredient Evaluation) that each of the ingredients makes a statistically significant contribution to the claimed effect. As long as "statistical significance" is shown, the Panel concludes that a contribution toward antidiarrheal effect will also have been shown to be clinically "significant."

3. Safety and effectiveness. In its consideration of active ingredients, the Panel reviewed the safety and effectiveness of all the combinations submitted. However, the Panel could not place any combination reviewed in Category I because of a lack of sufficient information concerning the safety and/or effectiveness of such ingredients as contained in the submitted combinations.

The Panel considers it important that the minimum effective dose be established for each ingredient in a combination product.

4. Single active ingredients. OTC drugs containing safe and effective single ingredients are preferred to

those having multiple active ingredients because of the reduced risks of toxic effects, synergistic effects, allergic and/or idiosyncratic reactions, and possible unrecognized and undesirable drug interaction(s).

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions.

5. Limitation of ingredients in antidiarrheal combination products. Given the paucity of effective antidiarrheal agents and the multiplicity of pathologic mechanisms causing common diarrhea, the Panel finds it difficult to define or restrict the total number of ingredients. However, in keeping with its conclusion that the fewer the ingredients the safer the combination, Category I combinations will be limited to 2 ingredients.

6. Active ingredients not reviewed by the Panel. Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and

consequently not found in this document, such ingredient is automatically classified as a Category II ingredient, i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration is required before a product containing such an ingredient may be marketed.

7. Review of submitted combination products. The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) and included above in paragraph A. The Panel recognizes that other combination products may be in the market place but it has either no knowledge of such products, or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel be evaluated through the new drug procedures, or be the subject of an appropriate petition to the Commissioner to review or amend the OTC antidiarrheal monograph.

8. Combinations containing nonantidiarrheal ingredients. Products combining antidiarrheal ingredient(s) with other ingredients having nonantidiarrheal pharmacologic effects are considered irrational, unless it can be shown that there is a significant target population requiring concurrent treatment of symptoms that require antidiarrheal(s) and nonantidiarrheal(s) in combination. The common symptoms of gastroenteritis would support the rationale of combining an antidiarrheal with an antiemetic or an agent for the treatment of gastritis but no such effective combination has been found.

Nonantidiarrheal ingredient(s) may be present as inactive ingredients in antidiarrheal products as an aid to formulation or to palatability. However, the presence of such ingredient(s) must not be emphasized or identified as active ingredients in the labeling or in the advertisement of such product(s).

9. Classification of submitted combinations. Within the categories defined by the Panel the combinations submitted for review are classified as follows:

Oral Dosage Forms

Category I combinations.

None yet designated.

Category II combinations.

a. Bismuth subsalicylate, phenyl salicylate (salol), and zinc phenolsulfonate.

b. Bismuth subsalicylate, precipitated calcium carbonate, and aminoacetic acid (glycine, glycocol).

c. Kaolin, pectin, hyoscyamine sulfate, atropine sulfate, scopolamine (hyoscine) hydrobromide, and powdered opium.

d. Kaolin, pectin, hyoscyamine sulfate, atropine sulfate, and scopolamine (hyoscine) hydrobromide.

e. Bismuth subnitrate, rhubarb fluidextract, potassium carbonate, and calcium hydroxide.

f. Activated attapulgite, pectin, and hydrated alumina powder.

g. Paregoric, pectin, and kaolin.

h. Kaolin, hydrated alumina powder, and pectin.

i. Tincture of opium, homatropine methylbromide, and pectin.

Category III combinations.

a. Lactobacillus acidophilus and sodium carboxymethylcellulose.

b. Lactobacillus acidophilus and lactobacillus bulgaricus.

c. Activated attapulgite and pectin.

d. Kaolin and pectin.

e. Tincture of opium and pectin.

f. Kaolin and hydrated alumina powder.

Rectal Dosage Forms

None yet designated.

10. Ingredients included in Category I combinations. Since there are presently no acceptable Category I combinations the Panel is setting forth guidelines whereby present and future Category I ingredients may reasonably be considered for a Category I combination. The Panel recommends:

a. The combination be limited to 2 Category I active antidiarrheal ingredients.

b. Each ingredient in the subject combination must be present within the dosage range for a Category I antidiarrheal ingredient, as set forth elsewhere in this document. The Panel recommends that the Food and Drug

Administration designate additional Category I antidiarrheal agents as appropriate safety and efficacy data become available.

c. The specific combination of ingredients must be an approved Category I combination. Since there are no Category I combinations presently designated, the Panel recommends that the Food and Drug Administration designate such combinations as appropriate safety and efficacy data become available.

11. Criteria for Category II combination products. A combination is classified by the Panel as a Category II product, i.e., one that is not generally recognized as safe and effective, if any of the following apply:

a. The combination contains 3 or more active antidiarrheal ingredients.

b. The combination contains any ingredient that is above the maximum dosage set for such agent as listed elsewhere in this document or in the future designated by the Food and Drug Administration for an antidiarrheal agent.

c. The combination contains any active antidiarrheal ingredient that has not been reviewed by the Panel and accordingly not listed in this document or in the future designated by the Food and Drug Administration.

12. Criteria for Category III combination products. A combination is classified as a Category III combination if any of the following apply:

a. If any Category I ingredient is below the minimum dosage range set by the Panel elsewhere in this document for such respective ingredient.

b. If 1 or more ingredient(s) are Category III ingredients, as set forth elsewhere in this document for single active antidiarrheal ingredients.

13. Reclassification requirements for Category III combinations to Category I combinations. a. For any Category III combination found in paragraph 9 where one or both ingredients fall below the minimum effective level as set forth elsewhere in this document for such individual ingredient(s), tests must be performed to substantiate the effectiveness of any such ingredient. The Panel recommends that such testing be pursued under the NDA procedures or petition to the Agency for appropriate modification of the monograph to permit such lower dosages.

b. (1) Any combination that contains one or both ingredients in Category III, as set forth elsewhere in this document, must be tested to satisfy Category I requirements for each such ingredient.

(2) Two Category I ingredients in a combination not found in paragraph 9 must be petitioned to the Agency for an appropriate amendment to the monograph or proceed through the NDA procedures.

14. Combinations containing nonantidiarrheal ingredients. Products combining antidiarrheal ingredient(s) with other ingredients having nonantidiarrheal pharmacologic effects are considered irrational, unless it can be shown that there is a significant target population requiring concurrent treatment of symptoms that require antidiarrheal(s) and nonantidiarrheal(s) in combination.

Nonantidiarrheal ingredient(s) may be present as inactive ingredients in antidiarrheal product as an

aid to formulation or to palatability. However, the presence of such ingredient(s) must not be emphasized or identified as active ingredients in the labeling or in the advertisement of such product(s).

H. Inactive Ingredients

When antidiarrheal products contain inactive ingredients, the Panel recommends that the inactive ingredients be listed on the label with or without the amounts contained in a recommended dose. The availability of sodium, potassium, and magnesium in the maximum recommended daily dose should be stated on the label. (See labeling discussion above for antidiarrheal products.) If significant amounts are present, special warnings on the label should be provided (as indicated previously in this document) for patients with heart disease and renal disease or those on a low salt diet.

I. Data Pertinent for Antidiarrheal Ingredient Evaluation

The Panel has given considerable thought to the problem of demonstrating that an antidiarrheal is safe and effective. When a drug is available for widespread use, as in OTC products, its safety and effectiveness must be well documented by toxicological data, data on the absorption, distribution, fate and excretion of the drug, the pharmacological effects of the drug, and the mechanism of action. The drug should also meet certain effectiveness standards.

The Panel recommends that information such as the following be obtained in the categories of data when relevant and pertinent to the drug under study: Toxicological data, absorption, distribution, fate, and excretion (ADFE) data, mechanism of action and effectiveness standards.

1. Toxicological data. A variety of toxicological data can be obtained to demonstrate that an antidiarrheal is safe. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the safety of their products. The Panel recommends that data such as the following be obtained in animal studies and in clinical studies

in man. Certain data on human subjects, such as lethal doses and chronic toxicity, will be available only from poison control centers, hospitals, medical centers, or medical examiners. However, the Panel considers such data important and attempts should be made to obtain them.

(a) Preclinical animal studies. (1) The oral LD_{50} established in no less than two animal species.

(2) Determinations of histologic and biochemical alterations in animals given lethal doses acutely or low doses chronically.

(3) Studies of teratogenicity and embryolethality. Studies of effects on fertility, delivery, and nursing offspring may also be indicated.

(b) Clinical studies. (1) Biochemical tests of liver and renal function and measurement of serum electrolytes after a therapeutic dose.

(2) Chronic toxicity studies in man, especially in relation to altered function and cytological changes of the mucosa of the intestinal tract of man.

(3) Adverse drug reactions should be well documented. Substantial effort should be made to have physicians document side effects, especially those of a serious nature as indicated

(4) Minimal lethal dose by single oral ingestion and in divided doses when such data are available from accidental or deliberate overdosing.

(5) Maximal tolerated dose from single oral ingestion, or divided multiple oral ingestions, when such data are available from accidental or deliberate overdosing.

2. Absorption, distribution, fate, and excretion (ADFE) as determined by currently accepted methods. Since ADFE bears directly on the safety of drugs and occasionally on the mechanism of action of antidiarrheals, appropriate data should be provided for all active ingredients and their active metabolic products. The methods for obtaining these data are established and are not different from those used in the study of ADFE of other drugs. Data such as the following would provide sufficient information regarding ADFE. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding ADFE of their products:

a. The percentages of various oral doses of the drug which are absorbed in man.

b. The percentages of various oral doses of the drug which are excreted in the urine in man.

c. The percentages of various oral doses of the drug which are excreted in breast milk.

d. The metabolic fate in man of absorbed but unexcreted drug.

e. The fate of unabsorbed drug in man.

f. The net bioavailability of the drug in man.

g. The ingredients and metabolic products associated with fecally excreted drug and/or its unabsorbed intraluminal biotransformation products.

h. The ingredients and metabolic products associated with renally excreted drug and/or its renally excreted biotransformation product.

3. Effects. The Panel recognizes that the mechanism of action of many safe and effective drugs is unknown. Nevertheless, data should be provided which serve to elucidate the pharmacologic effects of antidiarrheals. For example, if they are claimed to be adsorptive agents, adsorption must be documented. If the claim is based upon the effects of an

anticholinergic action on motility, appropriate methods should be used that will demonstrate the effects of the agent on intestinal or colonic motility. In addition, it is recommended that data such as the following be obtained. Manufacturers are not expected to obtain all of these data, but are expected to obtain those data relevant to the unanswered questions regarding the mode of action of their products:

a. Effects of oral drug on jejunal secretion and the flux of ions and water at the levels of jejunum, ileum, proximal and distal colon.

b. Effects of the oral drug on the absorption of actively transported ions, sugars, and amino acids.

c. Effects of the oral drug on the absorption of carbohydrate, protein, lipids and fat-soluble vitamins.

d. Effects of the oral drug on the absorption of other drugs.

e. Effects of the oral drug on secretion of gastrointestinal enzymes and hormones.

f. Effects on intestinal smooth muscle such as contractility and electromyographic changes.

4. Effectiveness standards. The effectiveness of antidiarrheal agents can be tested using patients with diarrheal disorders as occur in travel and commonly referred to as "Turista", or in institutionalized patients where periodic epidemic mild diarrhea may occur, or in outpatient clinics and pharmacies where pediatric and adult patients are frequently seen with diarrheal problems and in specific situations such as radiation diarrhea. Although antidiarrheal agents can be tested in both human and animal models where diarrhea has been induced, i.e., cholera model, the Panel questions the relevance of these to human disease states as related to nonspecific common diarrhea. Antidiarrheals may be of a number of different types. When the antidiarrheal product contains more than one active ingredient, the double-blind, Latin square, design is particularly suited for testing the effectiveness of individual ingredients as well as comparing their effect against that of placebo. When it is impossible or impractical to devise an acceptable placebo, the antidiarrheal ingredient may be compared with another acceptable agent and studied in parallel groups. When experimental models of induced diarrhea are used, each subject can serve as his own control, but the period of study should be sufficiently long to clearly demonstrate differences.

Specific parameters that can be measured quantitatively to determine the effectiveness of an antidiarrheal agent include many of those used for determining the effectiveness of a laxative agent. For an antidiarrheal agent, the following parameters would be considered appropriate for assessing the effectiveness of the agent. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the effectiveness of their products:

a. Frequency. The Panel recognizes that frequency of stool evacuation is quite variable among normal, healthy individuals and may range from three bowel movements per day to three per week. Frequency should be expressed in number of evacuations per unit time such as 24 hours or per week, etc.

b. Volume. The volume of stool evacuated during a unit time period is easy to determine and is usually expxpressed in milliliters or cubic centimeters per 24 hours or other time period. Average normal is 150 ml/24 hours.

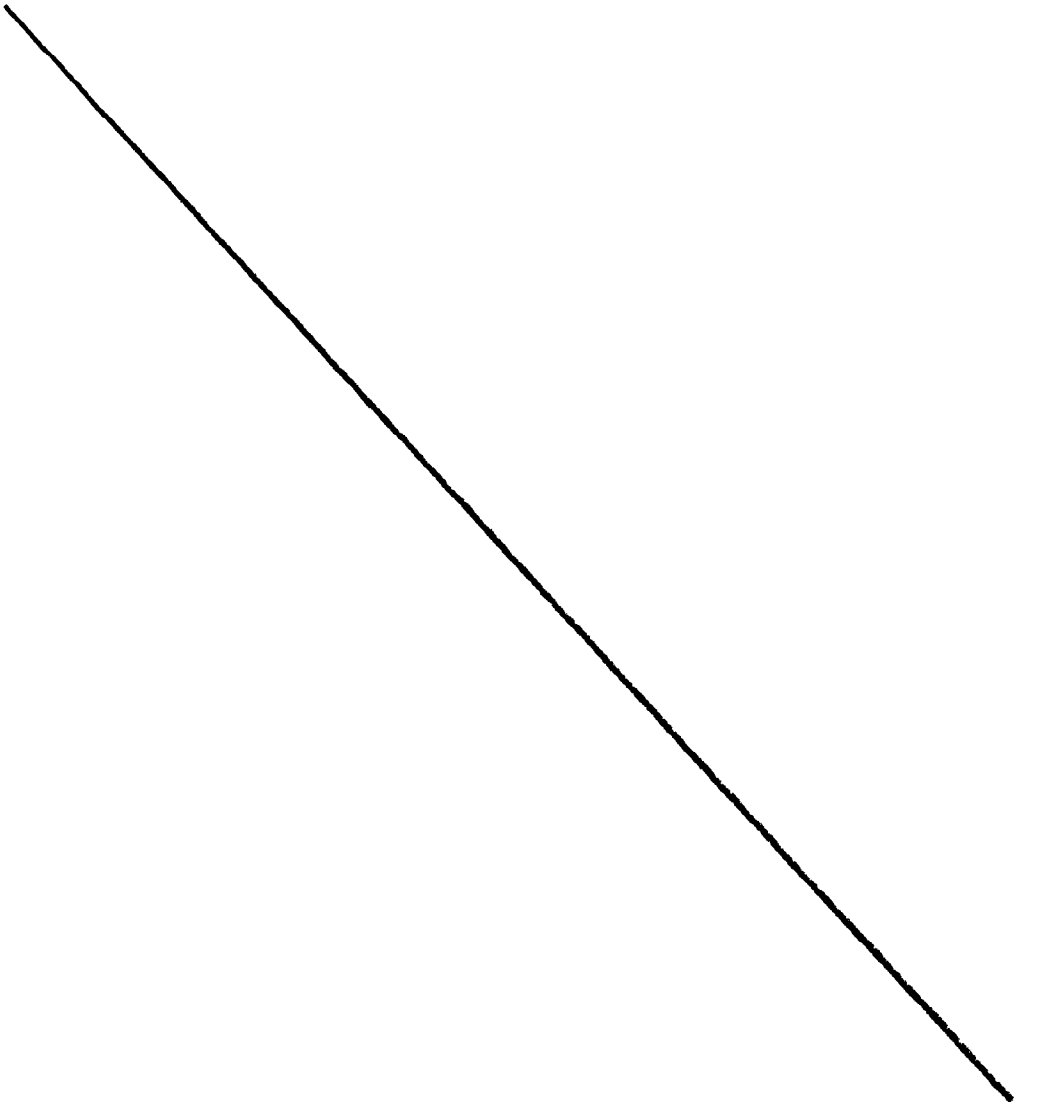
c. Weight. Weight of stool is expressed in grams per 24 hours or other unit time period. Weight is independent of consistency and important in determining the effectiveness of antidiarrheals. Average normal is 110 to 130 grams per 24 hours.

d. Water content. Water content of the feces is usually expressed as percent water. Excess water excretion is the hallmark of diarrhea and important in evaluating the effectiveness of antidiarrheals. Average normal is 60 to 85 percent. Since hydrophilic agents may decrease stool frequency and percent water content but actually increase the daily excretion of water and electrolytes, the combined information is particularly relevant to the effect of antidiarrheal in young children.

Because of the large variation in the water content of normal stools, measurement on stool water content for each subject before, during and after treatment become very important.

e. Consistency. Consistency should be evaluated in some objective manner in addition to the subject's sensation of ease of passage or the observer's description of the stool as liquid, soft, hard, etc. Since major changes in the consistency of stool (and other materials) may occur with little change in either percent water or total stool weight, the Panel recommends a quantitative determination of consistency. There are few rheologic studies of

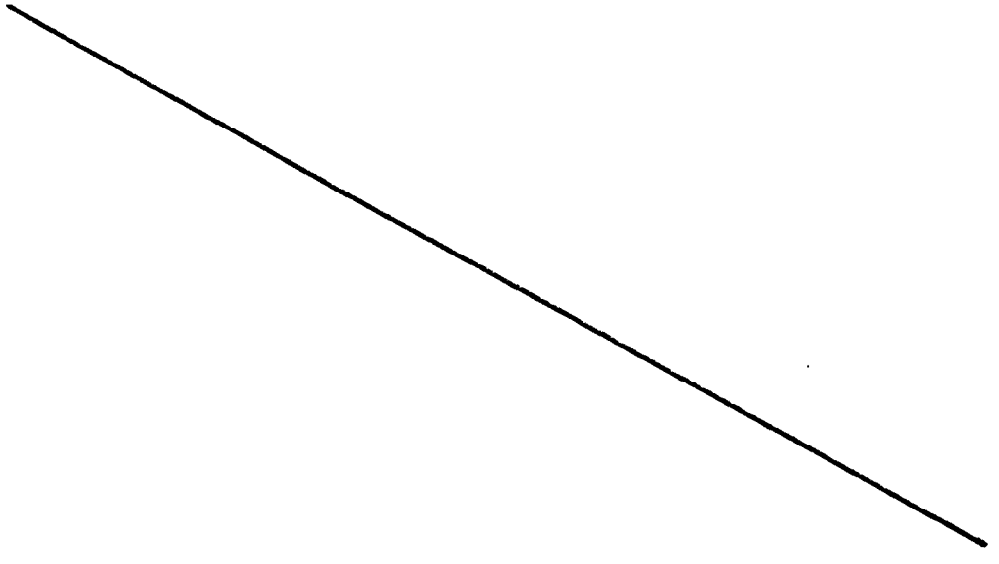
colonic content (Refs. 1 and 2) but instrumentation used to quantitate the consistency of compounds, such as bread doughs, various pastes, and soils might be appropriate. If a tube viscometer is used, consistency is expressed in terms of shear rate and if a penetrometer is used, consistency is expressed in terms of kilogram per square centimeter.



f. Fecal solids. Fecal solids are usually expressed in grams per 24 hours. Average normal is 25 grams/24 hours.

g. Bulk density. Bulk density is expressed as unit weight per unit volume, usually grams per cubic centimeter, and is determined by drying a known volume to a constant weight at 105° C. Bulk density is an important parameter in determining the effectiveness of bulk-forming laxatives. Average normal is 0.15 to 0.18 gm/cc.

h. Transit time. Transit time may be expressed by either the "time method" or the "distance method" by use of nonabsorbable markers such as polyethylene glycol, nonabsorbable color dyes such as carmine, and nonabsorbable radioactive materials such as chromium. In addition, inert colored plastic beads have been used as a marker to determine transit time. The use of some markers, such as carmine dye, is associated with considerable "streaming" and should be taken into account when markers are used to separate treatment periods. Average normal is 40 to 60 hours for complete transit of the digestive tract.



i. Fecal excretion rate. Fecal excretion rate is expressed in weight per unit time, usually grams per hour. Average normal fecal excretion rate is 6 grams per hour.

j. Stool electrolytes, bile salts, etc. Feces contain a number of substances that might be appropriate to measure in evaluating antidiarrheal agents. Stool electrolytes, particularly sodium, potassium and chloride, may be markedly altered by diarrhea and losses may be actually increased by antidiarrheals such as hydrophilic agents.

REFERENCES

(1) Picologlou, B.F., P.D. Patel, and P.S. Lykoudis, "Biorheological Aspects of Colonic Activity: Part I. Theoretical Considerations," Biorheology, 10:431-440, 1973.

(2) Picologlou, B.C., P.D. Patel and P.S. Lykoudis, "Biorheological Aspects of Colonic Activity: Part II. Experimental Investigation of Rheological Behavior of Human Feces." Biorhelogy, 10:441-446, 1973.

III. ANTIEMETICS

Pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) requesting the submission of data and information on OTC antiemetic drugs, the following firms made submissions relating to the indicated products:

A. Data and Information Submissions

FIRM	MARKETED PRODUCTS
Pfizer Pharmaceuticals, New York, NY 10017.	Bonine.
William H. Rorer, Inc., Fort Washington, PA 19034.	Emetrol.
Searle Laboratories, Chicago, IL 60680.	Dramamine, Dramamine Liquid.
Norwich Pharmaceutical Co., Norwich, NY 13815.	Pepto-Bismol Liquid, Pepto-Bismol Tablets.

B. The Labeled Ingredients Contained in Submitted Products

Aminoacetic acid (glycine, glycocol)

Bismuth subsalicylate

Dimenhydrinate

Meclizine hydrochloride

Orthophosphoric acid

Phenylsalicylate (salol)

Sugar (invert)

Zinc phenolsulfonate

The Panel also undertook a review of the following:

Cyclizine hydrochloride

C. Emesis and the Use of OTC Antiemetics

Severe nausea, and the realization that one is about to vomit, is one of the more dreadful conditions suffered by man. Motion sickness accompanied by nausea and vomiting is not unusual and may be prevented effectively by a number of antihistamine-like drugs available in OTC antiemetic products. Motion sickness occurs when visual and vestibular stimuli are not in accord, particularly when the head rotates in two axes simultaneously. Some individuals are more resistant to motion sickness than others, but none is immune. Travel aboard ship, in airplanes, or even in automobiles may induce motion sickness. OTC antiemetics are also needed for other causes of nausea and vomiting as in patients undergoing chemotherapy or radiation therapy for malignancy, and episodic vomiting of childhood.

D. Classification of Active Ingredients

The Panel reviewed all active ingredients which were the subject of submissions made to the Panel pursuant to the standards for safety, effectiveness, and truthful labeling.

In accordance with the regulation (21 CFR 330.10), the Panel's findings with respect to these ingredients are set forth in three categories:

I. Conditions under which antiemetic products are generally recognized as safe and effective and are not misbranded.

II. Conditions under which antiemetic products are not generally recognized as safe and effective or are misbranded.

III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel recommends for each class of drugs:

1. That the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the FEDERAL REGISTER.

2. That the conditions excluded from the monograph on the basis of the Panel's determination that they would result in the drug not being generally recognized as safe and effective or would result in misbranding (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph in the FEDERAL REGISTER,

regardless whether further testing is undertaken to justify their future use.

3. That the conditions excluded from the monograph on the basis of the Panel's determination that the available data are insufficient to classify such conditions either as generally recognized as safe and effective and not misbranded or as not being generally recognized as safe and effective or would result in misbranding (Category III) be permitted to remain in use for 2 years after the date of publication of the final monograph in the FEDERAL REGISTER, if the manufacturer or distributor of any such drug utilizing such conditions in the interim conducts tests and studies adequate and appropriate to satisfy the questions raised with respect to the particular condition by the Panel.

E. Review of Active Ingredients

All active ingredients which were the subject of submissions made to the Panel were carefully reviewed. The Panel considered all pertinent data and information available to the Panel in arriving at its conclusions and recommendations.

1. Conditions under which antiemetic products are generally recognized as safe and effective and are not misbranded. The following antiemetic ingredients were classified as safe and effective and not misbranded:

BENZHYDRYL PIPERAZINE ANTIHISTAMINES

Cyclizine

Meclizine

DIMENHYDRINATE

(a) Benzhydryl piperazine antihistamines--(1) Cyclizine and Meclizine. The Panel concludes that cyclizine and meclizine are safe and effective in the amounts taken orally (meclizine, for adults 25 to 50 milligrams once daily; and cyclizine, 50 milligrams up to 4 times daily and for children 6 to 12 years 25 mg up to 3 times daily) in antiemetic products for the treatment of nausea and vomiting of motion sickness.

Meclizine is a member of the benzhydryl piperazine group of antihistamine compounds which also includes cyclizine. Chemically, these compounds differ from other antihistamines in that the alkylamino group exists as a ring structure.

An extensive literature is available to support the conclusion that meclizine is effective and safe in the management of motion sickness (Refs. 1 through 5). The drug has a relatively long duration of action and is reported to afford 24-hour protection against the symptoms of motion sickness (Refs. 3 and 4).

Meclizine is relatively free of side effects when administered in therapeutic doses, although sedation (drowsiness) sometimes occurs and may be troublesome in those persons who

drive automobiles or operate other machinery. Containers of OTC meclizine tablets are labeled to warn of this potential hazard.

In 1966, the Food and Drug Administration acting on the recommendation of an Ad Hoc Advisory Committee, required relabeling of the OTC products containing meclizine and cyclizine to include the following warning: "Not for use by women who are pregnant or who may become pregnant, unless directed by a physician, since this drug may have the potentiality of injuring the unborn child." This labeling warning was prompted by concern that the drug may have teratogenic or embryolethal potential. The Panel has carefully reviewed more recent epidemiological data, the previous report of the FDA Ad Hoc Advisory Committee, and the position of the American Teratology Society regarding the limitations of extrapolating animal data to man (Ref. 6). The Panel concluded that the scientific data do not warrant a need to restrict the use of meclizine or cyclizine or require the labeling to include a pregnancy warning, but reevaluation may be needed as additional data become available.

The Panel reviewed data on 50,282 pregnant women of which 1,014 had used meclizine during the early stages of pregnancy. Data showed that the incidence of malformation of the offspring of the 1,014 women was not statistically increased over that of

the other 49,268 pregnant women not using meclizine, but who had used other drugs during pregnancy. Further, the Panel had indirect evidence that meclizine is not embryocidal and that the incidence of specific teratogenicity (e.g., cleft palate) was actually less in the data compiled from the use of meclizine in human pregnancies than that which might have been expected from the previous underlying animal studies which had led to the pregnancy warning (Ref. 7).

Labeling

A claim should be made only for the effectiveness of benzydryl piperazine group in the treatment of nausea and vomiting due to motion sickness. Claims for effectiveness for the treatment of nausea and vomiting of other causes have not been proven. The label should carry the warning that this drug can produce drowsiness and persons taking it should be cautioned regarding driving automobiles or operating heavy machinery or equipment. Specific warnings should also cite its anticholinergic action and patients with glaucoma or enlargement of the prostate gland should be cautioned regarding taking this OTC product other than under the direction of a physician. For cyclizines the label should also contain the following warning: "Do not give to children under 6 years of age except under the advice and supervision of a physician." For meclizine, the label should also contain the following warning: "Do not give to children under 12 years of age except under the advice and supervision of a physician."

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(6) Staples, R. E., "Teratogens and the Delaney Clause," Science, 185:813-814, 1974.

(7) Shapiro, S., Boston Children's Medical Center, Testimony Before OTC Laxative, Antidiarrheal, Emetic, and Antiemetic Panel, October 11, 1974.

(b) Other active ingredient-- Dimenhydrinate. The Panel concludes that 50 to 100 milligrams dimenhydrinate is safe and effective in the amounts usually taken orally in antiemetic products (200 mg to 400 mg daily in 4 divided doses) for the treatment of nausea and vomiting associated with motion sickness. The dosage for children 2 to 5 years of age is 12.5 to 25 mg up to 3 times daily and for children 6 years and over 25 to 50 mg up to 3 times daily.

Dimenhydrinate is the 8-chlorotheophyllin salt of the antihistamine diphenhydramine. Since introduction in 1949, the effectiveness of dimenhydrinate against seasickness and airsickness has been repeatedly demonstrated. Dimenhydrinate is relatively free of side effects when administered in recommended doses, although drowsiness sometimes occurs and may prove troublesome in individuals driving an automobile or operating other types of machinery.

LABELING

A claim should be made only for the effectiveness of dimenhydrinate in the treatment of nausea and vomiting due to motion sickness. The Panel is unaware of the existence of acceptable scientific data relating to claims for effectiveness in the treatment of nausea and vomiting from other causes. Such additional claims have not been proven.

The label should carry the warning that this drug can produce drowsiness and persons taking it should be cautioned regarding driving automobiles or operating heavy machinery or equipment. Specific warnings should also cite its anticholinergic action and patients with glaucoma or enlargement of the prostate gland should be cautioned regarding taking this OTC product other than under the direction of a physician.

REFERENCES

(1) Gay, L. N. and P. E. Carliner, "The Prevention and Treatment of Motion Sickness. I. Seasickness," Science, 109:359, 1949.

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2. Conditions under which antiemetic products are not generally recognized as safe and effective or are misbranded. The Panel found that there was no scientific or even sound theoretical basis for claimed effectiveness of a number of ingredients used in OTC antiemetic products. The Panel concludes that it is misleading to make claims regarding multiple indications for use of single ingredients when no evidence exists to support such claims.

The Panel further concludes that the following ingredient, should be removed from the market as an antiemetic agent unless and until further scientific testing supports its use:

INDIVIDUAL ACTIVE INGREDIENT

Aminoacetic acid (glycine, glycocol)

(a) Individual active ingredient--(1) Aminoacetic acid (glycine, glycocol). The Panel concludes that aminoacetic acid is safe in the amounts usually taken orally in antidiarrheal products, but there is no evidence to support tis effectiveness as an antiemetic agent.

The Panel can find no evidence to support the claim that glycine (identified in the Antacid Monograph) alone or in combination is an effective antiemetic or antinauseant. The claim that glycine is effective for the relief of "nausea," "indigestion," "gas," "fullness," "bloating," "pressure," and "upset stomach" is not supported by any carefully controlled clinical studies. Since hyperacidity is not a known cause of vomiting there is no sound theoretical or scientific basis to indicate that the addition of glycine to antiemetics would offer relief of the indicated symptoms.

3. Conditions for which the available data are insufficient to permit final classification at this time. The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the active ingredients listed below:

Bismuth subsalicylate

Phenyl salicylate (salol)

Phosphorated carbohydrate

Zinc phenolsulfonate

The Panel believes it reasonable to allow 2 years for the development and review of such evidence. Marketing need not cease during this time if adequate testing is undertaken. If data regarding adequate effectiveness and safety are not obtained within 2 years, however, the ingredients listed in this category should no longer be marketed as active ingredients in over-the-counter products but may be permitted as inactive ingredients if the amount employed is necessary for the pharmaceutical formulation of the product. Some ingredients may be present in products in quantities which are pharmacologically inactive by virtue of being subclinical doses. In these cases the ingredients may be included for pharmaceutical necessity such as improving the stability or palatability of the product. However, it is the opinion of the Panel that if an ingredient was originally claimed by the sponsor to be active, it cannot then also be claimed inactive and included for formulation purposes unless the following are documented: The absolute necessity for inclusion in the pharmaceutical formulation, the safety of the quantity in the finished product, and the inactivity of the quantity in the finished product.

The Panel has given careful consideration to the types of studies and types of data to be required for removing a claimed active antiemetic ingredient from Category III and placing it in Category I. See data required below for antiemetic ingredient evaluation. In general, to demonstrate effectiveness, the design of the study should have a sound scientific basis (e.g., a randomized, double-blind, cross-over study comparing claimed active ingredients to placebo), the clinical trial should be carefully controlled (e.g., consideration given to selection of subjects representative of general population as well as diet, activity, travel, etc. of subjects being studied), and quantitative measurement of various parameters appropriate for the claimed effects of the ingredient. To demonstrate safety, appropriate toxicological studies in experimental animals (preferably primate) and man are required as outlined elsewhere.

(a) Bismuth subsalicylate. The Panel concludes that bismuth subsalicylate is safe in the amounts usually taken (1 to 4 grams) orally. However, the Panel concludes that there is insufficient evidence to establish effectiveness of bismuth subsalicylate as an antiemetic.

Evidence available to the Panel indicates that emesis in dogs induced by 15 ml of ipecac syrup can be controlled effectively by pretreatment with 0.35 gm/kg of bismuth subsalicylate in a liquid preparation (Ref. 1). In human subjects, 1 ounce of a bismuth preparation was no better than 1 ounce of water in preventing emesis which had been induced by a dose of 15 ml of ipecac syrup.

Studies evaluating the effectiveness of bismuth compounds for "upset stomach" or "nausea" suffer from the vague definitions of these complaints. Bismuth compounds appear to control the uncomfortable feelings accompanying low doses of ipecac syrup, but whether pretreatment with bismuth (subsalicylate) followed by ipecac is an appropriate model for the consumer's "upset stomach" is debatable. It is difficult to postulate any effect of any drug on distention symptoms induced by overeating, unless it affects gastric emptying time, the tone of the stomach wall or intragastric pressure. However,

bismuth subsalicylate has been promoted for use to treat symptoms such as "indigestion", "gas", "full stomach", etc. The Panel concurs with the Commissioner of Food and Drugs when he noted in the tentative final order establishing the Antacid monograph published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260), that some of these symptoms are vague, and most are poorly understood (Ref. 2).

Labeling

Special labeling should indicate that stools may become dark with use of any bismuth compound.

Date Pertinent for Effectiveness

Bismuth is not promoted as an antimotion sickness agent, thus, motion sickness models would not be appropriate for this agent.

Vomiting induced by the oral administration of ipecac, pepper sauce, mustard, or potassium chloride are suggested models for the claim of antiemesis. The investigator using these models should ensure that patients not be pretreated with bismuth.

A model must be developed that approximates the upper gastrointestinal symptoms produced by food intolerance, and it must produce these sensations with some reliability and

measure of objectivity. The Panel is unable to define such claims as "upset stomach," and "distention". Accordingly, the Panel cannot appropriately suggest a model to test the effectiveness of bismuth for such claims.

The Panel concurs with the conclusions of the OTC antacid Panel set forth in the proposal published in the FEDERAL REGISTER of April 5, 1973 (38 FR 8714) that such claims provide evidence of effectiveness. The evidence should consist of statistically valid clinical trials to support each of the respective claims. (See paragraph G below for data pertinent for antiemetic ingredient evaluation.)

REFERENCES

(1) OTC Volume 090123.[1/]

(2) "Tentative Final Order for Antacid Products," published in the FEDERAL REGISTER of November 12, 1973 (38 FR 31260).

(b) Phenyl salicylate (salol). The Panel concludes that salol is safe in the amounts usually taken orally in OTC products, but there is no evidence to support its effectiveness as an antiemetic agent.

The Panel can find no evidence to support the claim that salol alone or in combination is an effective antiemetic or antinauseant. The claim that phenyl salicylate is effective for the relief of "nausea," "indigestion," "gas," "fullness," "bloating," "pressure," and "upset stomach" is not supported by any carefully controlled clinical studies.

Data Pertinent for Effectiveness

Well-controlled, double-blind clinical trials are needed to compare the antiemetic effect of phenylsalicylate, alone and if desired in combination, as compared with placebo and with an effective antiemetic. Documentation is needed of the blood salicylate levels 1 hour after ingestion. The response should be evaluated by objective changes in frequency of vomiting. Careful experimental design, definition of terms and matching of subjects is needed to assess the effect on subject complaints of malaise and nausea. (See paragraph G below for data pertinent for antiemetic ingredient evaluation.)

(c) Phosphorated carbohydrate (levulose-dextrose-ortho-phosphoric acid). The Panel concludes that phosphorated carbohydrate is safe in the amounts usually taken (8 to 18 grams) orally. However, the Panel concludes that there is insufficient evidence to establish effectiveness of phosphorated carbohydrate as an antinauseant-antiemetic.

Phosphorated carbohydrate preparation consists of a solution containing invert sugar (a mixture of equimolar amounts of levulose and dextrose obtained by hydrolysis of sucrose) and phosphoric acid which is used to adjust the pH of the solution to a range of 1.5 to 1.6.

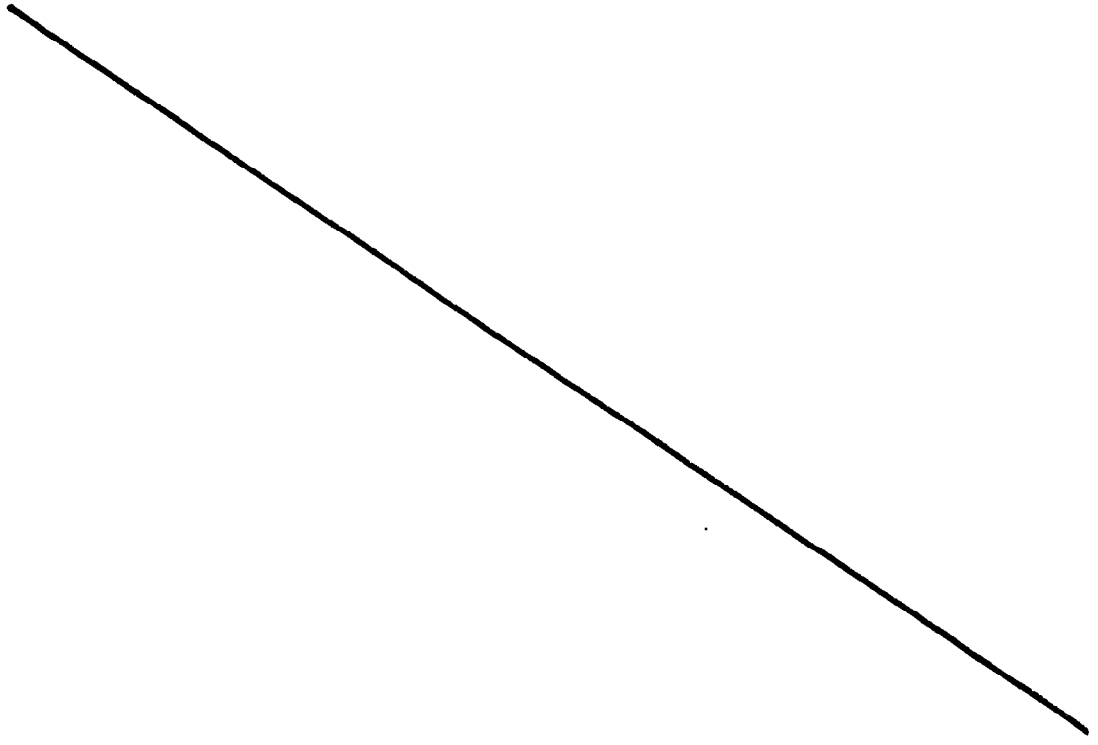
A mechanism that has been cited in support of the belief that a carbohydrate-phosphoric acid mixture relieves nausea and vomiting is its potential to inhibit gastric emptying as a consequence of inhibition of gastric peristalsis and a reduction in gastric tone. It has been reported that the high osmotic pressure exerted by concentrated solutions of simple sugars (monosaccharides) inhibits gastric emptying through an action on duodenal osmoreceptors which are

sensitive to high osmotic pressures (Ref. 1). However, a positive correlation between an increase in gastric emptying time and relief of nausea and vomiting has not been established.

Only a few clinical studies have been reported on the use of a carbohydrate-phosphoric acid preparation for the management of nausea and vomiting. Most of these were either uncontrolled or partially controlled investigations (Refs. 2 through 4). In the only double-blind clinical investigation, the study was poorly designed (Ref. 5).

Data Pertinent for Effectiveness

The Panel concludes that well-controlled, properly designed clinical studies are needed to establish the effectiveness of the carbohydrate-phosphoric acid solution for the control of nausea or vomiting. (See paragraph G below for data pertinent for anti-emetic ingredient evaluation.)



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(2) Bradley, J. E., L. Proutt, E. R. Shipley and R. H. Oster, "An Evaluation of Carbohydrate-Phosphoric Acid Solution in the Management of Vomiting", Journal of Pediatrics, 38:41-44, 1951.

(3) Crunden, A. B., Jr. and W. A. Davis, "The Oral Use of a Phosphorated Carbohydrate Solution in Nausea and Vomiting of Pregnancy," American Journal of Obstetrics and Gynecology, 65:311-313, 1953.

(4) Tebrock, H. E. and M. M. Fisher, "Nausea and Vomiting: Evaluation of an Orally Administered Phosphorated Carbohydrate Solution," Medical Times, 82:271-275, 1954.

(5) Agerty, H. A., "A Phosphorated Carbohydrate Solution for the Prevention of Motion Sickness," Adult and Child, 1:66, 1969.

(d) Zinc phenolsulfonate. The Panel concludes that zinc phenolsulfonate is safe in amounts usually taken orally in OTC products, but there is no evidence to support its effectiveness as an antiemetic agent.

The Panel can find no evidence to support the claim that zinc phenolsulfonate alone or in combination in OTC products is an effective antiemetic or antinauseant. The claim that zinc phenolsulfonate is effective for the relief of "nausea," "indigestion," "gas," "fullness," "bloating," "pressure," and "upset stomach" is not supported by any carefully controlled clinical studies.

Data Pertinent for Effectiveness

Well-controlled, double-blind clinical trials are needed to compare the antiemetic effect of zinc phenolsulfonate, alone and if desired in combination, as compared with placebo and with an effective antiemetic. The response should be evaluated by objective changes in frequency of vomiting. Careful experimental design, definition of terms, and matching of subjects is needed to assess the effect on subject complaints of malaise and nausea. (See paragraph G below for data pertinent for antiemetic ingredient evaluation.)

F. Products Containing Multiple Antiemetic Ingredients

1. General statements. a. The Panel noted the regulation (21 CFR 330.10(a)(4)(iv)) which states:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients, and when the combination, when used under adequate direction for use, and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

b. The Panel concludes that, in general, the fewer the ingredients, the safer and more rational the therapy. The Panel believes that the interests of the consumer are best served by exposing the user of OTC drugs to the fewest ingredients possible at the lowest possible dosage regimen consistent with a satisfactory level of effectiveness.

c. The Panel further concludes that OTC drugs should contain only such inactive ingredients that are necessary for pharmaceutical formulation.

2. Requirement of significant contribution. The Panel has further determined that each claimed active ingredient in the combination must make a significant contribution to the claimed effect. In the absence of data showing the minimum dose necessary to achieve the intended antiemetic effect, the amount of ingredient present in antiemetic products must be at least equal to the currently accepted minimum dose range for such active ingredients as set forth elsewhere in this document.

The Panel found it difficult to quantitate the contribution of each antiemetic ingredient in combinations, as is possible with antacid combination products, for example, where the contribution of each antacid can be determined by chemical titration. Further, the minimum effective dose may vary considerably with the cause of the vomiting.
The Panel recognizes that it is possible that some ingredients may be proved to contribute to the effectiveness of a combination product in amounts below the generally

recognized minimum effective daily dose.

The Panel concluded that where a combination product is permitted, it is sufficient to demonstrate in well-controlled clinical trials that each of the ingredients makes a statistically significant contribution to the claimed effect. As long as "statistical significance" is shown, the Panel concludes that a contribution toward antiemesis will also have been shown.

3. Single active ingredients. OTC drugs containing safe and effective single ingredients are preferred to those having multiple active ingredients because of the reduced risks of toxic effects, synergistic effects, allergic and/or idiosyncratic reactions, and possible unrecognized and undesirable drug interaction(s).

It is an established medical principle to give only those medications, preferably as single entities, necessary for the safe and effective treatment of the patient. This principle applies equally to self-medication. To add needlessly to the patient's medication increases the risk of adverse reactions.

4. Active ingredients not reviewed by the Panel. Each claimed active ingredient must be an ingredient that has been reviewed by the Panel. If a product contains an active ingredient that has not been reviewed by the Panel and consequently not found in this document, such ingredient is automatically classified as a Category II ingredient, i.e., it is not generally recognized as safe and/or effective. Appropriate animal and human testing and prior approval by the Food and Drug Administration is required before a product containing such an ingredient may be marketed.

5. Review of submitted combination products. The Panel considered only those combination products submitted pursuant to the notice published in the FEDERAL REGISTER of February 8, 1973 (38 FR 3614) and included above in paragraph The Panel recognizes that other combination products may be in the market place but it has either no knowledge of such products, or insufficient data with respect to such products to make a reasonable judgment of safety and/or effectiveness.

Accordingly, the Panel recommends that any new combination, or any presently marketed combination not submitted to this Panel be evaluated through the new drug procedures, or be the subject of an appropriate petition to the Commissioner to review or amend the OTC antiemetic monograph.

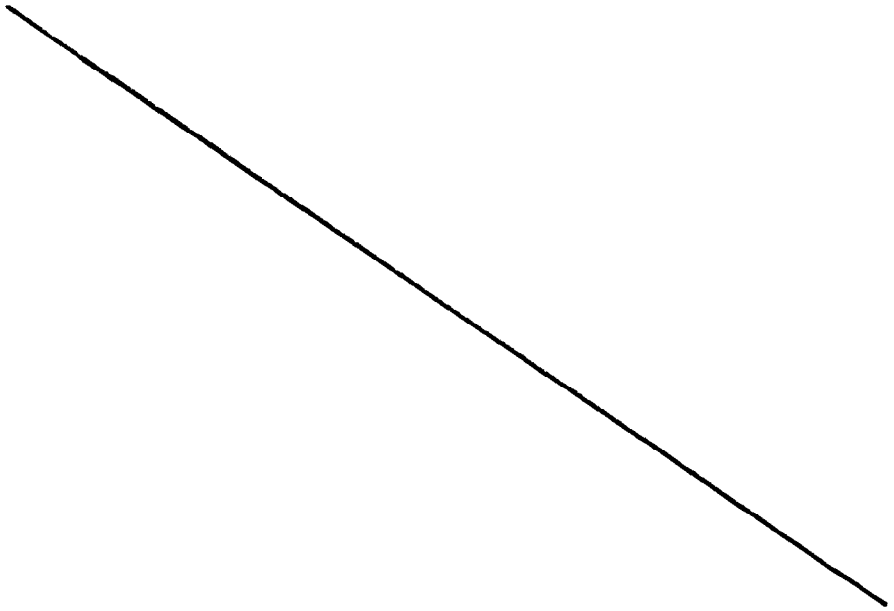
6. Category II combination product. The Panel concludes that combinations of bismuth subsalicylate, aminoacetic acid, phenyl salicylate, and zinc phenolsulfonate are safe in the amounts usually taken orally in OTC combination products, but there is no evidence that each of these four ingredients makes a significant contribution to the claimed antiemetic action of such combination.

Further, because any combination containing a Category II ingredient is classified as a Category II combination, the above combination is deemed a Category II product.

G. Data Pertinent for Antiemetic Ingredient Evaluation

When a drug is available for widespread use, as in OTC products, its safety and effectiveness must be well documented by toxicological data, data on the absorption, distribution, fate and excretion of the drug, the pharmacological effects of the drug, and the mechanism of action. The drug should also meet certain effectiveness standards. The Panel recommends that information such as the following be submitted when relevant and pertinent to the drug under study: Toxicological data, absorption, distribution, fate and excretion (ADFE) data, pharmacological effects, and effectiveness standards.

1. Toxicological data. A variety of toxicological data can be obtained to demonstrate that an antiemetic is safe. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding the safety of their products. The Panel recommends that data such as the following be required



in preclinical animal studies and in clinical studies in man. Certain data on humans, such as lethal doses and chronic toxicity, will only be available from poison control centers, hospitals, medical centers, or medical examiners. However, the Panel considers such data important and attempts should be made to obtain them.

(a) Preclinical animal studies. (1) The oral LD_{50} should be established in several animal species.

(2) Determinations must be made to detect histologic and biochemical alterations in animals given lethal doses acutely or low doses chronically.

(3) Studies of teratogenicity and embryolethality are necessary. Studies of effects on fertility, delivery, and nursing offspring may also be indicated.

(b) Clinical studies in man. (1) Biochemical tests of liver and renal function and measurement of serum electrolytes after a therapeutic dose.

(2) Chronic toxicity studies in man.

(3) A clear record of unwanted drug effects. Substantial effort should be made to have physicians document side effects, especially those of serious nature.

(4) Minimal lethal dose by single oral ingestion and in divided doses when such data are available from accidental or deliberate overdosing.

(5) Maximal tolerated dose from single oral ingestion, or divided multiple oral ingestions, when such data are available from accidental or deliberate overdosing.

2. Absorption, distribution, fate and excretion (ADFE) as determined by currently accepted methods. Since ADFE bears directly on the safety of drugs and occasionally on the mechanism of action, appropriate data should be provided for all active ingredients and their metabolic products. The method for obtaining these data are established and are not different from those used in the study of other drugs. Data such as the following would provide sufficient information regarding ADFE. Manufacturers are not expected to obtain all of the following data, but are expected to obtain these data relevant to the unanswered questions regarding ADFE of their products:

a. The percentages of various oral doses of the drug which are absorbed in man.

b. The percentages of various oral doses of the drug which are excreted in the urine in man.

c. The metabolic fate in man of absorbed but unexcreted drug including studies on placental transfer and breast milk excretion.

d. The fate of unabsorbed drug in man.

e. The net bioavailability of the drug in man.

f. The ingredients and metabolic products associated with fecally excreted drug and/or its unabsorbed intraluminal biotransformation products.

g. The ingredients and metabolic products associated with renally excreted drug and/or its renally excreted biotransformation product.

3. Effects. The Panel recognizes the lack of physiological data on the gastrointestinal receptors and effectors of emesis and the related difficulty in establishing the mechanism of action of agents acting on either the central or autonomic nervous system or directly affecting gastric motility or tone. However, data should be provided which serve to elucidate the pharmacologic effects of antiemetic agents. The Panel recommends that data such as the following be obtained. Manufacturers are not expected to obtain all of the following data, but are expected to obtain those data relevant to the unanswered questions regarding pharmacologic effects of their products:

a. Effects of oral drug on nausea and vomiting.

b. Effects of oral drug on cardiovascular system (blood pressure and heart rate).

c. Effects of oral drug on autonomic nervous system.

d. Duration of oral drug effects.

e. Effects on drowsiness and the central nervous system.

4. Effectiveness standards. Motion sickness, which may occur when visual and vestibular stimuli are not in accord, may be induced by a number of techniques. Unusual motion patterns in which the head is rotated in two axes simultaneously will produce motion sickness in anyone; some individuals are more resistant than others, but none is immune. Motion sickness may also be induced when the body is stationary and the individual looks at a motion picture film as seen from an airplane doing acrobatics or a roller coaster ride (Ref. 1). Thus, a number of experimental models are available to test the effectiveness of antiemetic agents advocated for nausea and vomiting resulting from motion sickness. Both normal individuals and subjects with known susceptibility to motion sickness could be tested. The

threshold of stimulus (duration in time, rotation rate in r.p.m., and acceleration rate) to induce motion sickness should be determined before and after the test drug is administered to determine degree of effectiveness and duration of time of protection from motion sickness. Comparisons should be made using the double-blind technique, with placebo and a known effective agent such as scopolamine. Manufacturers are not expected to obtain all of the data listed above, but are expected to obtain those data relevant to the unanswered questions regarding the effectiveness of their products. The effectiveness of drugs in vomiting due to causes other than motion sickness requires well-controlled clinical trials in homogenous groups of subjects with vomiting of relatively specific types such as that of radiation sickness, epidemic food or chemical poisoning, post-operative vomiting, epidemic gastroenteris, etc.

The experimental design for testing effectiveness of antiemetic may be of a number of different types. When the antiemetic product contains more than one active ingredient, the double-blind, Latin square, cross-ver design is particularly suited for testing the effectiveness of individual ingredients as well as comparing their effect against that of placebo. When it is impossible or impractical to devise an acceptable placebo, the antiemetic ingredient may be compared with

another acceptable agent and studied in parallel groups. When experimental models of induced diarrhea are used, each subject can serve as his own control, but the period of study should be sufficiently long to clearly demonstrate differences.

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